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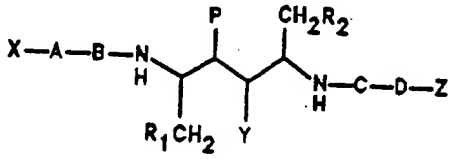

(I)

(57) Abstract

The present invention provides novel peptides of formula (I). These peptides are useful as inhibitors of retroviral proteases. Inhibitors of retroviral proteases, such as the HIV-I protease, are useful for treating diseases caused by retroviruses, such as human acquired immunodeficiency disease syndrome (AIDS).

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PEPTIDES CONTAINING SUBSTITUTED 1,4-DIAMINES AS TRANSITION-STATE INSERTS

DESCRIPTION

BACKGROUND OF THE INVENTION

The present invention provides novel compounds. More particularly, the present invention provides novel peptide analogs. The peptides of the present invention contain a substituted 1,4-diamine moiety as a novel transition state insert. These peptides are useful as inhibitors of retroviral proteases. Inhibitors of retroviral proteases, such as the HIV-I protease, are useful for treating diseases caused by retroviruses, such as human acquired immunodeficiency disease syndrome (AIDS).

BACKGROUND OF THE INVENTION

An estimated one to one and one-half million people in the United States are infected with a human retrovirus, the human immunodeficiency virus type I, HIV-1, which is the etiological agent of acquired immunodeficiency syndrome, AIDS (C. Norman, Science, 661-662 (1986)). Of those infected, an estimated two hundred and fifty thousands people will develop AIDS in the next five years (J.W. Curran, et al., Science, 1352-1357 (1985)). On March 20, 1987, the FDA approved the use of the compound, zidovudine (AZT), to treat AIDS patients with a recent initial episode of pneumocystis carinii pneumonia, AIDS patients with conditions other than pneumocystis carinii pneumonia or patients infected with the virus with an absolute CD4 lymphocyte count of less than 200/mm^3 in the peripheral blood. AZT is a known inhibitor of viral reverse transcriptase, an enzyme necessary for human immunodeficiency virus replication.

U.S. Patent 4,724,232 claims a method of treating humans having acquired immunodeficiency syndrome utilizing 3'-azido-3'-deoxy-thymidine (azidothymidine, AZT).

Since the first description of the malady in the early part of this decade, acquired immunodeficiency disease syndrome (AIDS) and its devastating consequences have been subjects of continuous and intense coverage in both the lay and scientific press. Indeed, a recent edition of Scientific American was entirely devoted to AIDS (Scientific American 289, #4 (1988)), and the literature on the disease and the virus is already so vast as to defy thorough citation. At present, there is no effective treatment of the disease, and 3'-azido-3'-deoxythymidine (AZT), an inhibitor of the viral reverse

transcriptase (RT) remains the therapy of choice, despite its highly toxic side effects.

Human immunodeficiency virus (HIV) has long been recognized as the causative agent in AIDS, although a minority opinion to the contrary has been expressed (e.g., P. Duesberg, Proc. Natl. Acad. Sci., USA, 86:755-764 (1989)). Sequence analysis of the complete genomes from several infective and non-infective HIV-isolates has shed considerable light on the make-up of the virus and the types of molecules that are essential for its replication and maturation to an infective species (L. Ratner, et al., Nature, 313:277-284 (1985)). HIV exhibits the same gag/pol/env organization seen in other retroviruses (L. Ratner, et al., Nature, 313:277-284 (1985)); S. Wain-Hobson, et al., Cell, 40:9-17 (1985); R. Sanchez-Pescador, et al., Science, 227:484-492 (1985); and M.A. Muesing, et al., Nature, 313: 450-458 (1985)).

Reverse transcriptase (RT) is an enzyme unique to retroviruses that catalyzes the conversion of viral RNA into double stranded DNA. Blockage at any point during the transcription process, by AZT or any other aberrant deoxynucleoside triphosphate incapable of elongation, should have dramatic consequences relative to viral replication. Much work on the RT target is in progress based, in large measure, upon the fact that nucleosides like AZT are easily delivered to cells. However, the inefficiency of phosphorylation steps to the triphosphate, and the lack of specificity and consequent toxicity, constitute major drawbacks to use of AZT and similar nucleosides having a blocked, or missing, 3'hydroxyl group.

The T4 cell receptor for HIV, the so-called CD4 molecule, has also been targeted as an intervention point in AIDS therapy (R.A. Fisher, et al., Nature, 331:76-78 (1988); R.E. Hussey, et al., Nature, 331:78-81 (1988); and K.C. Deen, et al., Nature, 331:82-84 (1988)). The exterior portion of this transmembrane protein, a molecule of 371 amino acids (sCD4) has been expressed in Chinese hamster ovary (CHO) cells and Genentech (D.H. Smith, et al., Science, 238:1704-1707 (1987)) has had a product in clinical trials since the fall of 1987. Thus far, little information on efficacy is available beyond the fact that the recombinant sCD4 appears to be relatively non-toxic. The idea behind CD4 based therapy is that the molecules can neutralize HIV by interfering with viral attachment to T4, and other cells which express CD4 on their surfaces. A variant on this theme is to attach cell toxins to CD4 for specific binding and delivery to infected cells which display glycoprotein gp-120 on their surfaces (M.A. Till, et al., Science, 242:1166-1168 (1988); and V.K. Chaudhary, et al., Nature, 335:369-372 (1988)).

Another therapeutic target in AIDS involves inhibition of the viral protease (or proteinase) that is essential for processing HIV-fusion polypeptide precursors. In HIV and several other retroviruses, the proteolytic maturation of the gag and gag/pol fusion polypeptides (a process indispensable for generation of infective viral particles) has been shown to be mediated by a protease that is, itself, encoded by the pol region of the viral genome (Y. Yoshinaka, et al., Proc. Natl. Acad. Sci. USA, 82:1618-1622 (1985); Y. Yoshinaka, et al., J. Virol., 55:870-873 (1985); Y. Yoshinaka, et al., J. Virol., 57:826-832 (1986); and K. von der Helm, Proc. Natl. Acad. Sci., USA, 74:911-915 (1977)).

The protease (or proteinase), consisting of only 99 amino acids, is among the smallest enzymes known, and its demonstrated homology to aspartyl proteases such as pepsin and renin (L.H. Pearl and W.R. Taylor, Nature, 329: 351-354 (1987); and I. Katoh, et al., Nature, 329:654-656 (1987)), led to inferences regarding the three-dimensional structure and mechanism of the enzyme (L.H. Pearl and W.R. Taylor, Nature, 329:351-354 (1987)) that have since been borne out experimentally. Active HIV protease has been expressed in bacteria (see, e.g., P.L. Darke, et al., J. Biol. Chem., 264:2307-2312 (1989)) and chemically synthesized (J. Schneider and S.B. Kent, Cell, 54:363-368 (1988); and R.F. Nutt, et al., Proc. Natl. Acad. Sci., USA, 85:7129-7133 (1988)). Site directed mutagenesis (P.L. Darke, et al., J. Biol. Chem., 264: 2307-2312 (1989); and N.E. Kohl, et al., Proc. Natl. Acad. Sci., USA, 85:4686-4690 (1988) and pepstatin inhibition (P.L. Darke, et al., J. Biol. Chem., 264:2307-2312 (1989); S. Seelmeier, et al., Proc. Natl. Acad. Sci., USA, 85:6612-6616 (1988); C.-Z. Giam and I. Borsos, J. Biol. Chem., 263:14617-14720 (1988); and J. Hansen, et al., EMBO J., 7:1785-1791 (1988)) have provided evidence for HIV protease's mechanistic function as an aspartyl protease. A recent study has demonstrated that the protease cleaves at the sites expected in peptides modeled after the regions actually cleaved by the enzyme in the gag and pol precursor proteins during viral maturation (P.L. Darke, et al., Biochem. Biophys. Res. Communs., 156:297-303 (1988)). X-ray crystallographic analysis of the HIV-protease (M.A. Navia, et al., Nature, 337:615-620 (1989)) and a related retroviral enzyme from Rous sarcoma virus (M. Miller, et al., Nature, 337:576-579 (1989)) reveal an active site in the protease dimer that is identical to that seen in other aspartyl proteases, thus supporting the supposition (L.H. Pearl and W.R. Taylor, Nature, 329:351-354 (1987)) that the HIV enzyme is active as a dimer.

To date, a compound which effectively inhibits retroviruses in a human hosting

such a virus, and thereby effectively treats diseases caused by such a virus, such as acquired immunodeficiency syndrome (AIDS), has not been found.

INFORMATION DISCLOSURE

D.J. Kempf et al., J. Med. Chem. 1990, 33, 2687-2689 discloses HIV protease inhibitors having the structures BOC-NH-CH(benzyl)-CH(OH)-CH(OH)-CH(benzyl)-NH-BOC and Cbz-Val-NH-CH(benzyl)-CH(OH)-CH(OH)-CH(benzyl)-NH-Val-Cbz. This article was published prior to the filing date of the present application, but after the invention herein.

European patent application 189,203, published 30 July 1986, and European patent application 230,266, published 24 July 1987, disclose N-dihydroxyalkyl peptide derivatives which are useful as inhibitors of renin for treating hypertension. They specifically disclose the intermediate compound, (2S,3R,4S)-1-amino-2,3-dihydroxy-4-*tert*-butoxy-carbonylamino-5-cyclohexylpentane, and the final compound Boc-Phe-His Amide of (2S,3R,4S)-1-(3-Methylbutylcarbonylamino)-2,3-dihydroxy-4-amino-5-cyclohexylpentane.

Derivatives of isosteric bond replacements at positions 10,11 as dihydroxy ethylene isosteres are disclosed in International Patent Application, PCT/US87/00291, published 11 September 1987 (Publication No. WO87/05302).

International Patent Application, PCT/US 87/03007, published 30 June 1988 (Publication No. WO88/04664) discloses renin inhibitory peptides having an epoxide or glycol moiety at the 10,11-position.

International Application PCT/US90/03754, filed 9 July 1990, discloses peptides having a diamino glycol moiety as the non-cleavable transition state insert corresponding to the 10,11-position of the renin substrate (angiotensinogen). These peptides are disclosed as being useful as renin inhibitors and as inhibitors of retroviral proteases.

U.S. Patent Application Serial No. 07/573,110, filed 24 August 1990, discloses peptides, having amino-polyols as transition state mimics, which are useful as renin inhibitors and retroviral protease inhibitors.

The inhibition by relatively high concentrations of pepstatin A (100 μM), a general aspartyl proteinase inhibitor, of HIV replication in H9 cells is described in K. Von der Helm, et al., FEBS Letters, 247:349 (1989).

Great Britain 2,203,740 (Sandoz) claims the use of renin inhibitors for treating diseases caused by retroviruses.

A.D. Richards, et al., FEBS Letters, 247:113 (1989) discloses tBoc-His-Pro-Phe-His-LVA-Ile-His, a potent inhibitor of another aspartyl protease human renin, which also contains a hydroxyethylene isotere, inhibits the HIV-1 protease in vitro.

Recent information from Smith-Kline-Beecham researchers has described work on the inhibition of HIV-1 replication in cell culture with synthetic protease inhibitors. Int. AIDS Symposium, Montreal, Canada, June 1989

The following patent applications disclose peptides that are useful as inhibitors of renin and HIV-I protease: International application, Serial No. PCT/US89/01672, filed 24 April 1989; U.S. Patent application, Serial No. 07/405,691, filed 11 September 1989; and International application, Serial No. PCT/US90/03754, filed 9 July 1990..

SUMMARY OF THE INVENTION

The present invention particularly provides:

A compound of Formula I

wherein X is

(a) hydrogen,

(b) C_1-C_7alkyl,

(c) aryl-$(CH_2)_p$-,

(d) Het-$(CH_2)_p$-,

(e) C_3-C_7cycloalkyl-$(CH_2)_p$-,

(f) R_5-O-CH_2-C(O)-,

(g) R_5-CH_2-O-C(O)-,

(h) R_5-O-C(O)-,

(i) R_5-$(CH_2)_n$-C(O)-,

(j) R_5-$(CH_2)_n$-C(S)-,

(k) $R_4N(R_4)$-$(CH_2)_n$-C(O)-

(l) R_5-SO_2-$(CH_2)_q$-C(O)-,

(m) R_5-SO_2-$(CH_2)_q$-O-C(O)-,

(n) R_6-$(CH_2)_n$-C(O)-, or

(o) R_5-$(CH_2)_n$-SO_2-;

wherein Z is

(a) hydrogen,

(b) C_1-C_7alkyl,

(c) -$(CH_2)_p$-aryl,

(d) $-(CH_2)_p$-Het,

(e) $-(CH_2)_p$-C_3-C_7cycloalkyl,

(f) $-C(O)-CH_2-O-R_5$,

(g) $-C(O)-O-CH_2-R_5$,

(h) $-C(O)-O-R_5$,

(i) $-C(O)-(CH_2)_n-R_5$,

(j) $-C(S)-(CH_2)_n-R_5$,

(k) $-C(O)-(CH_2)_n-(R_4)NR_4$,

(l) $-C(O)-(CH_2)_q-SO_2-R_5$,

(m) $-C(O)-O-(CH_2)_q-SO_2-R_5$,

(n) $-C(O)-(CH_2)_n-R_6$, or

(o) $-SO_2-(CH_2)_n-R_5$;

wherein P is OH or NH_2;

wherein Y is OH or NH_2;

wherein Q is

(a) $-CH_2-$,

(b) -CH(OH)-,

(c) -O-, or

(d) -S-;

wherein A or B or both are absent or are a divalent moiety of the formula XL_1, XL_2 or XL_3 or other amino acyl derivative;

wherein C or D or both are absent or are a divalent moiety of the formula XL_4, XL_5 or XL_6 or other amino acyl derivative;

wherein R_1 is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) aryl,

(d) C_3-C_7cycloalkyl,

(e) -Het,

(f) C_1-C_3alkoxy, or

(g) C_1-C_3alkylthio;

wherein R_2 is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) aryl,

(d) C_3-C_7cycloalkyl,

(e) -Het,

(f) C_1-C_3alkoxy, or

(g) C_1-C_3alkylthio;

wherein R_3 is

(a) hydrogen,

(b) C_1-C_5alkyl, or

(c) aryl-C_1-C_5alkyl;

wherein R_4 is

(a) hydrogen

(b) C_1-C_5alkyl,

(c) $-(CH_2)_p$-aryl,

(d) $-(CH_2)_p$-Het,

(e) $-(CH_2)_p$-C_3-C_7cycloalkyl, or

(f) 1- or 2-adamantyl;

wherein R_5 is

(a) C_1-C_6alkyl,

(b) $-(CH_2)_p$-C_3-C_7cycloalkyl,

(c) $-(CH_2)_p$-aryl,

(d) $-(CH_2)_p$-Het, or

(e) 5-oxo-2-pyrrolidinyl;

wherein R_6 is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) $-(CH_2)_p$-aryl,

(d) $-(CH_2)_p$-Het,

(e) $-(CH_2)_p$-C_3-C_7cycloalkyl, or

(f) 1- or 2-adamatyl;

wherein R_7 is

(a) hydrogen,

(b) C_1-C_3alkyl, or

(c) phenyl-C_1-C_3alkyl;

wherein R_8 is

(a) hydrogen,

(b) C_1-C_5 alkyl, or

(c) -$(CH_2)_p$-phenyl;

wherein m is 1 to 2, inclusive

wherein n is 0 to 5, inclusive;

wherein p is 0 to 2, inclusive;

wherein q is 1 to 5, inclusive;

wherein aryl is phenyl or naphthyl substituted by zero to three of the following:

(a) C_1-C_3alkyl,

(b) hydroxy,

(c) C_1-C_3alkoxy,

(d) halo,

(e) amino,

(f) mono- or di-C_1-C_3alkylamino,

(g) -CHO,

(h) -COOH,

(i) $COOR_7$,

(j) $CONHR_7$,

(k) nitro,

(l) mercapto,

(m) C_1-C_3alkylthio,

(n) C_1-C_3alkylsulfinyl,

(o) C_1-C_3alkylsulfonyl,

(p) -$N(R_8)$-C_1-C_3alkylsulfinyl,

(q) SO_3H,

(r) SO_2NH_2,

(s) -CN, or

(t) CH_2NH_2;

wherein -Het is a 5- or 6-membered saturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a

benzene ring or another heterocycle; and if chemically feasible, the nitrogen and sulfur atoms may be in the oxidized forms; and optionally substituted by zero to three of the following:

(a) C_1-C_5alkyl,
(b) hydroxy,
(c) hydroxy (C_1-C_5alkyl),
(d) halogen,
(e) amino,
(f) amino (C_1-C_5alkyl),
(g) -CHO,
(h) $-CO_2H$,
(i) $-CO_2$-(C_1-C_5alkyl),
(j) $-CONH_2$,
(k) -CONH-(C_1-C_5alkyl),
(l) nitro,
(m) mercapto,
(n) mercapto (C_1-C_5alkyl),
(o) $-SO_3H$,
(p) $-SO_2NH_2$,
(q) -CN, or
(r) -O-C_1-C_5alkyl;

or a carboxy, amino or other reactive group protected form thereof;

or a pharmaceutically acceptable acid or base addition salt thereof.

By "amino acyl derivatives" is meant any of the naturally occurring amino acids such as: glycine, alanine, valine, leucine, isoleucine, phenylalanine, lysine, proline, tryptophan, methionine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, arginine, ornithine, and histidine, and synthetic derivatives thereof. These compounds may be in the L or D configuration and are well known and readily available to those skilled in the art.

The present invention provides for novel compounds or pharmacologically acceptable salts and/or hydrates thereof. Pharmacologically acceptable salts refers to those salts which would be readily apparent to a manufacturing pharmaceutical chemist to be equivalent to the parent compound in properties such as formulation, stability,

patient acceptance and bioavailablility.

Examples of pharmaceutically acceptable acid addition salts include: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethane-sulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate.

The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix (C_i-C_j) indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus (C_1-C_4)alkyl refers to alkyl of one to 4 carbon atoms, inclusive, or methyl, ethyl, propyl, butyl, and isomeric forms thereof. C_4-C_7cyclic amino indicates a monocyclic group containing one nitrogen and 4 to 7 carbon atoms.

Examples of (C_3-C_{10})cycloalkyl, which include alkyl-substituted cycloalkyl containing a total of up to 10 total carbon atoms, are cyclopropyl, 2-methylcyclopropyl, 2,2-dimethylcyclopropyl, 2,3-diethylcyclopropyl, 2-butylcyclopropyl, cyclobutyl, 2-methylcyclobutyl, 3-propylcyclobutyl, cyclopentyl, 2,2-dimethylcyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl and isomeric forms thereof.

Examples of aryl include phenyl, naphthyl, (o-, m-, or p-)tolyl, (o-, m-, or p-)ethylphenyl, 2-ethyl-tolyl, 4-ethyl-o-tolyl, 5-ethyl-m-tolyl, (o-, m-, or p-)propylphenyl, 2-propyl-(o-, m-, or p-)tolyl, 4-isopropyl-2,6-xylyl, 3-propyl-4-ethylphenyl, (2,3,4- 2,3,6-, or 2,4,5-)trimethylphenyl, (o-, m-, or p-)fluorophenyl, (o-, m-, or p-trifluoromethyl)phenyl, 4-fluoro-2,5-xylyl, (2,4-, 2,5-, 2,6-, 3,4-, or 3,5-)difluorophenyl, (o-, m-, or p-)chlorophenyl, 2-chloro-p-tolyl, (3-, 4-, 5- or 6-)chloro-o-tolyl, 4-chloro-2-propylphenyl, 2-isopropyl-4-chlorophenyl, 4-chloro-3-fluorophenyl, (3- or 4-)chloro-2-fluorophenyl, (o-, m-, or p-)trifluoro-methylphenyl, (o-, m-, or p-)ethoxyphenyl, (4- or 5-)chloro-2-methoxy-phenyl, and 2,4-dichloro(5- or 6-)methylphenyl, and the like.

Examples of -Het include: 2-, 3-, or 4-pyridyl, imidazolyl, indolyl, N^{in}-formyl-indolyl, N^{in}-C_1-C_5alkyl-C(0)-indolyl, 1,2,4-triazolyl, 2-, 4-, or 5-pyrimidinyl, 2- or 3-thienyl, piperidinyl, pyrryl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidi-

nyl, imidazolinyl, imidazolidinyl, pyrazinyl, piperazinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, and benzothienyl. Each of these moieties may be substituted as noted above.

As would be generally recognized by those skilled in the art of organic chemistry, a heterocycle as defined herein for -Het would not be bonded through oxygen or sulfur or through nitrogen which is within a ring and part of a double bond.

Halo is halogen (fluoro, chloro, bromo, or iodo) or trifluoromethyl.

Examples of pharmaceutically acceptable cations include: pharmacologically acceptable metal cations, ammonium, amine cations, or quaternary ammonium cations. Especially preferred metal cations are those derived from the alkali metals, e.g., lithium, sodium, and potassium, and from the alkaline earth metals, e.g., magnesium and calcium, although cationic forms of other metals, e.g., aluminum, zinc, and iron are also within the scope of this invention. Pharmacologically acceptable amine cations are those derived from primary, secondary, or tertiary amines.

The novel peptides herein contain both natural and synthetic amino acid residues. These residues are depicted using standard amino acid abbreviations (see, e.g., IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN), "Nomenclature and Symbolism for amino Acids and Peptides," Eur. J. Biochem. 138:9-37 (1984)) unless otherwise indicated.

As is apparent to those of ordinary skill in the art, the compounds of the present invention can occur in several diastereomeric forms, depending on the configuration around the asymmetric carbon atoms. All such diastereomeric forms are included within the scope of the present invention. Preferably, the stereochemistry of the amino acids corresponds to that of the naturally occurring amino acids.

The HIV protease, which belongs to the class of aspartyl proteases, is a C-2 symmetric homodimer, M.A. Navia et al., Science 1989, 337, 615; A. Wlodawer et al., Science 1989, 337, 616. Advantageously, the compounds of the present invention of formula I have C-2 symmetry and thus provide complementary ligands for the C-2 symmetric active site of the enzyme. In formula I, the C-2 symmetric transition-state insert is depicted at -NH-CH(CH_2R_1)-CHP-CHY-CH(CH_2R_2)-NH-. For the compounds of the present invention, the symmetrical transition-state inserts, 1,4-diamino-2,3-

dihydroxy-1,4-dibenzyl-butane and 1,4-diamino-2,3-dihydroxy-1,4-diisobutyl-butane, are preferred. The 1S,2S,3S,4S and the 1S,2R,3R,4S isomers are preferred.

The compounds of the present invention are effective and potent inhibitors of HIV protease. Therefore, the compounds of formula I inhibit retroviral proteases and thus inhibit the replication of the virus. They are useful for treating patients infected with a human retrovirus, such as human immunodeficiency virus (strains of HIV-1 or HIV-2) or human T-cell leukemia viruses (HTLV-I or HTLV-II) which results in acquired immunodeficiency syndrome (AIDS) and/or related diseases.

The capsid and replicative enzymes (i.e. protease, reverse transcriptase, integrase) of retroviruses are translated from the viral gag and pol genes as polyproteins that are further processed by the viral protease (PR) to the mature proteins found in the viral capsid and necessary for viral functions and replication. If the PR is absent or nonfunctional, the virus cannot replicate. The retroviral PR, such as HIV-1 PR, has been found to be an aspartic protease with active site characteristics similar to those exhibited by the more complex aspartic protease, renin.

The term human retrovirus (HRV) includes human immunodeficiency virus type I, human immunodeficiency virus type II, or strains thereof, as well as human T cell leukemia virus 1 and 2 (HTLV-1 and HTLV-2) or strains apparent to one skilled in the art, which belong to the same or related viral families and which create similar physiological effects in humans as various human retroviruses.

Patients to be treated would be those individuals: 1) infected with one or more strains of a human retrovirus as determined by the presence of either measurable viral antibody or antigen in the serum and 2) in the case of HIV, having either a symptomatic AIDS defining infection such as i) disseminated histoplasmosis, ii) isopsoriasis, iii) bronchial and pulmonary candidiasis including pneumocystic pneumonia iv) non-Hodgkin's lymphoma or v) Kaposi's sarcoma and being less than sixty years old; or having an absolute CD4 lymphocyte count of less than $200/m^3$ in the peripheral blood. Treatment would consist of maintaining an inhibitory level of the peptide used according to this invention in the patient at all times and would continue until the occurrence of a second symptomatic AIDS defining infection indicates alternate therapy is needed.

More specifically, an example of one such human retrovirus is the human immunodeficiency virus (HIV, also known as HTLV-III or LAV) which has been recognized as the causative agent in human acquired immunodeficiency disease syndrome

(AIDS), P. Duesberg, Proc. Natl. Acad. Sci. USA, 86:755 (1989). HIV contains a retro viral encoded protease, HIV-I protease, that cleaves the fusion polypeptides into the functional proteins of the mature virus particle, E.P. Lillehoj, et al., J. Virology, 62:3053 (1988); C. Debuck, et al., Proc. Natl. Acad. Sci., 84:8903 (1987). This enzyme, HIV-I protease, has been classified as an aspartyl protease and has a demonstrated homology to other aspartyl proteases such as renin, L.H. Pearl, *et al.*, Nature 329:351 (1987); I. Katoh, *et al.*, Nature 329:654 (1987). Inhibition of HIV-I protease blocks the replication of HIV and thus is useful in the treatment of human AIDS, E.D. Clerq, J. Med. Chem. 29:1561 (1986). Inhibitors of HIV-I protease are useful in the treatment of AIDS.

Pepstatin A, a general inhibitor of aspartyl proteases, has been disclosed as an inhibitor of HIV-I protease, S. Seelmeier, *et al.*, Proc. Natl. Acad. Sci. USA, 85:6612 (1986). Other substrate derived inhibitors containing reduced bond isosteres or statine at the scissle position have also been disclosed, M.L. Moore, *et al.*, Biochem. Biophys, Res. Commun. 159:420 (1989); S. Billich, *et al.*, J. Biol. Chem. 263:17905 (1988); Sandoz, D.E. 3812-576-A.

Thus, the peptides of the present invention are useful for treating diseases caused by retroviruses, such as human acquired immunodeficiency disease syndrome (AIDS). For this indication, the compounds of formula I are administered by oral, nasal, transdermal and parenteral (including i.m. and i.v.) routes in doses of 1 μg to 100 mg/kg of body weight.

Those skilled in the art would know how to formulate the compounds of this invention into appropriate pharmaceutical dosage forms. Examples of the dosage forms include oral formulations, such as tablets or capsules, or parenteral formulations, such as sterile solutions.

The compounds of the present invention are preferably orally administered to humans to effect HIV protease inhibition for the purpose of favorably treating diseases caused by retroviruses. For this purpose, the compounds are administered from 0.1 mg to 100 mg per kg per dose, from 1 to 4 times daily.

Either solid or fluid dosage forms can be prepared for oral administration. Solid compositions are prepared by mixing the compounds of this invention with conventional ingredients such as talc, magnesium stearate, dicalcium phosphate, magnesium aluminum silicate, calcium sulfate, starch, lactose, acacia, methyl cellulose, or functionally similar

pharmaceutical diluents and carriers. Capsules are prepared by mixing the compounds of this invention with an inert pharmaceutical diluent and placing the mixture into an appropriately sized hard gelatin capsule. Soft gelatin capsules are prepared by machine encapsulation of a slurry of the compounds of this invention with an acceptable inert oil such as vegetable oil or light liquid petrolatum. Syrups are prepared by dissolving the compounds of this invention in an aqueous vehicle and adding sugar, aromatic flavoring agents and preservatives. Elixirs are prepared using a hydroalcoholic vehicle such as ethanol, suitable sweeteners such as sugar or saccharin and an aromatic flavoring agent. Suspensions are prepared with an aqueous vehicle and a suspending agent such as acacia, tragacanth, or methyl cellulose.

When the compounds of this invention are administered parenterally, they can be given by injection or by intravenous infusion. An effective amount is from about 1 μg to 100 mg per kg per day. Parenteral solutions are prepared by dissolving the compounds of this invention in water and filter sterilizing the solution before placing in a suitable sealable vial or ampule. Parenteral suspensions are prepared in substantially the same way except a sterile suspension vehicle is used and the compounds of this invention are sterilized with ethylene oxide or suitable gas before it is suspended in the vehicle.

The exact route of administration, dose, or frequency of administration would be readily determined by those skill in the art and is dependant on the age, weight, general physical condition, or other clinical symptoms specific to the patient to be treated.

Patients to be treated would be those individuals: 1) infected with one or more than one strain of a human immunodeficiency virus as determined by the presence of either measurable viral antibody or antigen in the serum and 2) having either a symptomatic AIDS defining infection such as i) disseminated histoplasmosis, ii) isoporiasis, iii) bronchial and pulmonary candidiasis including pneumocystis pneumonia, iv) non-Hodgkin's lymphoma, or v) Kaposi's sarcoma and being less than sixty years old; or having an absolute CD4 lymphocyte count of less than 200/mm^3 in the peripheral blood. Treatment would consist of maintaining an inhibitory level of the compounds of this invention in the patient at all times and would continue until the occurrence of a second symptomatic AIDS defining infection indicates alternate therapy is needed.

The utility of the compounds of the present invention has been demonstrated in the biological test described below.

The HIV-1 protease has been expressed in E. coli, isolated, characterized and used to determine the inhibitory constants (K_I) of potential inhibitory compounds as follows:

The synthetic peptide H-Val-Ser-Gln-Asn-Tyr-Pro-Ile-Val-OH serves as the substrate for the measurement of HIV-1 protease activity. This peptide corresponds to the sequence from residue 128 to 135 in the HIV gag protein. Cleavage of the synthetic peptide, as well as the gag protein, takes place at the Tyr-Pro bond. HIV-1 protease activity is measured at 30°C in 50 mM sodium acetate, pH 5.5, containing 10% glycerol, 5% ethylene glycol, 0.1% Nonidet P-40 and 2.8 mM substrate in a total volume of 50 μl. After 30 minutes of incubation, 75 μl of 1% trifluoroacetic acid (TFA) is added and the reaction mixture subjected to HPLC analysis. HPLC is carried out with a Vydac C_{18} column (0.46 x 15 cm), eluting with a linear gradient of 0-30% acetonitrile over a period of 25 minutes at a flow rate of 1.0 ml/minute.

The K_I values of the compounds of formula I of the present invention are listed in Table I below.

The compounds of the present invention are also useful for treating non-human animals infected with a retrovirus, such as cats infected with feline leukemia virus. Other viruses that infect cats include, for example, feline infectious peritonitis virus, calicivirus, rabies virus, feline immunodeficiency virus, feline parvovirus (panleukopenia virus), and feline chlamydia. Exact dosages, forms and modes of administration of the compounds of the present invention to non-human animals would be apparent to one of ordinary skill in the art, such as a veterinarian.

The compounds of the present invention are prepared as depicted in the charts and as described more fully in the Preparations and Examples. In these charts, the variables are as defined above.

CHART A

Chart A describes the preparation of the insert of formula A-7 and final compounds of formulas A-8 and A-9 of Examples 1 and 2 below, respectively.

An aldol addition reaction between the aldehyde of formula A-1, prepared as described in S. Thaisrivongs et al., J. Med. Chem. 1987, 30, 976, as an epimeric mixture at C-2, and the acyloxazolidinone of formula A-2 lead to a mixture of two adducts, the compound of formula A-3 and its diastereomer. The chiral auxiliary is removed from the compound of formula A-3 by basic hydrolysis with hydrogen peroxide

to give the acid of formula A-4. A Curtius reaction using diphenylphosphoryl azide gives an intermediate isocyanate which is trapped by the adjacent hydroxyl group to give the cyclic carbamate of formula A-5. Vigorous basic hydrolysis of the compound of formula A-5 gives the hydroxyamine of formula A-6. The acid labile protecting groups are removed with acidic methanol to give the compound of formula A-7 which is isolated as the dihydrochloride. The compound of formula A-7 is treated with excess di-*tert*-butyldicarbonate to give the final peptide of formula A-8. The amine dihydrochloride A-7 can also be coupled with *tert*-butyloxycarbonyl-L-valine using diethylphosphoryl cyanide, by the procedure described in S. Yamada et al., Tetrahedron Lett. 1973, 1595, to give the final peptide of formula A-9.

Chart B

Chart B describes the preparation of the final peptide of formula B-4 of Example 3 below.

The amine dihydrochloride B-1, prepared as the compound A-7 in Chart A, can be coupled with *tert*-butyloxycarbonyl-N^{im}-tosyl-L-histidine using diethylphosphoryl cyanide by the procedure described in S. Yamada et al., Tetrahedron Lett. 1973, 1595, to give the compound of formula B-2. The *tert*-butyloxycarbonyl protecting group is removed with trifluoroacetic acid and the resulting amine is then coupled to 1-naphthoxyacetic acid using diethylphosphoryl cyanide, by the procedure described in S. Yamada et al., Tetrahedron Lett. 1973, 1595,to give the compound of formula B-3. The tosyl protecting group is then removed with 1-hydroxybenzotriazole to give the final peptide of formula B-4.

Chart C

Chart C describes the preparation of the insert of formula C-7 and final peptide of formula C-8 of Example 4 below.

An aldol addition reaction as described in C.H. Heathcock et al., J. Org. Chem. 1980, 45, 1727, between the aldehyde of formula C-1, also the compound of formula A-1 of Chart A, prepared as described in S. Thaisrivongs et al., J. Med. Chem. 1987, 30, 976, and the ester of formula C-2 gives the two adducts, the compound of formula C-3(A) and its diastereomer of formula C-3(B). Basic hydrolysis of the ester of formula C-3(A) gives the corresponding acid of formula C-4(A). A Curtius reaction using diphenylphosphoryl azide, by the procedure described in T. Shioiri et al., J. Am. Chem. Soc. 1972, 94, 6203, gives an intermediate isocyanate which is trapped by the adjacent

hydroxyl group to give the cyclic carbamate of formula C-5. Vigorous basic hydrolysis of the compound of formula C-5 gives the hydroxyamine of formula C-6. The acid labile protecting groups are removed with acidic methanol to give the compound of formula C-7 which is isolated as the dihydrochloride. The amine dihydrochloride of formula C-7 can be coupled with *tert*-butyloxycarbonyl-L-valine using bis(2-oxo-3-oxazolidinyl)phosphinic chloride, by the procedure described in J. Diago-Meseguer and A.L. Palomo-Coll, Synthesis 1980, 547, to give the final peptide of formula C-8.

Following procedures analogous to those described above, the other peptides of the present invention may be prepared.

Generally, the renin inhibiting polypeptides may be prepared by solution phase peptide synthetic procedures analogous to those described hereinafter or to those methods known in the art. Appropriate protecting groups, reagents, and solvents for the solution phase method can be found in "The Peptides: Analysis, Synthesis, and Biology," Vols. 1-5, eds. E. Gross and T. Meienhofer, Academic Press, NY, 1979-1983; "The Practice of Peptide Synthesis", M. Bodansky and A. Bodansky, Springer-Verlag, New York, 1984; "The Principles of Peptide Synthesis", M. Bodansky, Springer-Verlag, New York, 1984. Thus, for example, the carboxylic moiety of N^{α}-t-butyloxycarbonyl (BOC)-substituted amino acid derivatives having suitable side chain protecting groups, if necessary, may be condensed with the amino functionality of a suitably protected amino acid or peptide using a conventional coupling protocol such as dicyclohexyl-carbodiimide (DCC) and 1-hydroxybenzotriazole (HOBT) or diethylphosphoryl cyanide (DEPC) and triethylamine (Et_3N) in methylene chloride or dimethylformamide.

Following coupling reaction completion, the N^{α}-BOC moiety may be selectively removed with 50% trifluoroacetic acid with or without 2% anisole (v/v) in methylene chloride. Neutralization of the resultant trifluoroacetate salt may be accomplished with 10% diisopropylethylamine or sodium bicarbonate in methylene chloride.

Variations in the above description for starting materials, reactants, reaction conditions and required protecting groups to obtain other such N-alkylated compounds are known to an ordinarily skilled chemist or are readily available in the literature.

The compounds of the present invention may be in either free form or in protected form at one or more of the remaining (not previously protected) peptide, carboxyl, amino, hydroxy, or other reactive groups. The protecting groups may be any of those known in the polypeptide art. Examples of nitrogen and oxygen protection

groups are set forth in T.W. Greene, Protecting Groups in Organic Synthesis, Wiley, New York, (1981); J.F.W. McOmie, ed. Protective Groups in Organic Chemistry, Plenum Press (1973); and J. Fuhrhop and G. Benzlin, Organic Synthesis, Verlag Chemie (1983). Included among the nitrogen protective groups are t-butoxycarbonyl (BOC), benzyloxycarbonyl, acetyl, allyl, phthalyl, benzyl, benzoyl, trityl and the like.

The following compounds of the present invention are preferred:

4S,7S-Bis-[N^{α}-Benzyloxycarbonyl-L-valyl-amino]-5S,6S-dihydroxy-2,9-dimethyldecane;

4S,7S-Bis-[N^{α}-Benzyloxycarbonyl-L-valyl-amino]-5R,6S-dihydroxy-2,9-dimethyldecane.

4S,7S-Bis-[N^{α}-*tert*-Butyloxycarbonyl-L-valyl-amino]-5S,6S-dihydroxy-2,9-dimethyldecane;

4S,7S-Bis-[1-Naphthoxyacetyl-L-histidyl-amino]-5S,6S-dihydroxy-2,9-dimethyl-decane;

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following Preparations and Examples illustrate the present invention.

In the Preparations and Examples below and throughout this document:

^{1}H-NMR is nuclear magnetic resonance

BOC is t-butoxycarbonyl

BOPCL is bis (2-oxo-3-oxazolidinyl) phosphinic chloride

Bz is benzyl

C is centigrade

Cbz is benzyloxycarbonyl

$CDCl_3$ is deuteriochloroform

Celite is a filter aid

DCC is dicyclohexylcarbodiimide

DEPC is diethylphosphoryl cyanide

Et0Ac is ethyl acetate

g is grams

γ-Glu is γ-glutamic acid

His is histidine

N-MeHis is Nα-methyl histidine

HOBT is 1-hydroxybenzotriazole monohydrate

HPLC is high performance liquid chromatography

IR is infrared spectra

M or mol is mole

Me is methyl

min is minute

mL is milliliter

MPLC is medium pressure liquid chromatography

MS is mass spectroscopy

Ph is phenyl

Phe is phenylalanine

Pro is proline

TEA is triethylamine

TFA is trifluoroacetic acid

THF is tetrahydrofuran

TLC is thin layer chromatography

Tos is p-toluenesulfonyl

TsoH is p-toluenesulfonic acid

Tyr is tyrosine

(OCH_3)Tyr is O-methyl tyrosine

β-Val is β-Valine.

The wedge-shape line indicates a bond which extends above the plane of the paper relative to the plane of the compound thereon.

The dotted line indicates a bond which extends below the plane of the paper relative to the plane of the compound thereon.

Preparation 1 4S-Benzyl-3-(1-oxo-4-methylpentyl)-2-oxazolidinone (Formula A-2) Refer to Chart A.

To a stirred solution of 3.0 g of 4S-benzyl-2-oxazolidinone in 34 mL of dry tetrahydrofuran at -78°C under argon is added dropwise 11.9 mL of a 1.56 M solution of *n*-butyllithium in hexane. After 5 min, 2.8 mL of 4-methylvaleryl chloride is added and the resulting solution allowed to warm to room temperature. After 1 h, the reaction mixture is concentrated and the residue partitioned between ether and diluted aqueous sodium hydroxide. The organic phase is washed with saturated aqueous sodium chloride, dried (magnesium sulfate) and then concentrated. The residue is flash-chromatographed

on silica gel with 20% ethyl acetate in hexane to give 4.58 g of the title product as a colorless oil.

Physical characteristics of the title product are as follows:

^{1}H-NMR ($CDCl_3$) δ 0.95, 1.6, 2.76, 2.9, 3.3, 4.2, 4.7, 7.3.

Preparation 2 — 3-[3S-[3-(*tert*-Butyloxycarbonyl)-2,2-dimethyl-4S-isobutyl-5S-oxazolidinyl]-3-hydroxy-2S-isobutyl-1-oxopropy]-4S-benzyl-2-oxazolidinone (Formula A-3) Refer to Chart A.

To a stirred solution of 2.1 g of the title product of Preparation 1 in 3.8 mL of dichloromethane at 0°C under argon is added dropwise 8.3 mL of a 1 M solution of dibutylboron triflate in dichloromethane, followed by 1.6 mL of diisopropylethylamine. After stirring for 30 min, the reaction mixture is cooled to -78°C and 1.98 g of the epimeric mixture of aldehyde A-1 in 3.8 mL of dichloromethane is added with two 0.5 mL dichloromethane rinses. After 30 min, the reaction mixture is allowed to warm to room temperature and, after additional 2 h, it is cooled to 0°C. A 5.1 mL portion of 1 M aqueous phosphate pH 7 buffer is added, followed by 10.2 mL of methanol, and 5.1 mL of 30% hydrogen peroxide in 10.2 mL of methanol. After stirring at 0°C for 3 h, the reaction mixture is partitioned between dichloromethane and aqueous phosphate pH 7 buffer. The organic phase is dried (magnesium sulfate) and then concentrated. The residue is flashed chromatographed on silica gel with 25% to 30% ethyl acetate in hexane to give 0.76 g of the title product, and 2.96g of the other diastereomer.

Physical characteristics of the title product are as follows:

^{1}H-NMR ($CDCl_3$), δ 0.9, 1.47, 1.54, 1.58, 2.70, 3.36, 4.17, 4.7, 7.3.

FAB MS $[M+H]^+$=561. Anal., 65.72% C, 8.75 % H, 4.99% N.

IR 2960, 1785, 1700, 1385 cm^{-1}.

Physical characteristics of the other diastereomer are as follows:

^{1}H NMR δ 0.9, 1.46, 2.7, 2.9, 3.3, 3.7, 4.2, 4.7, 7.2.

Preparation 3 — 3-[3S-[3-(*tert*-Butyloxycarbonyl)-2,2-dimethyl-4S-isobutyl-5S-oxazolidinyl]-3-hydroxy-2S-isobutyl-propionic acid (Formula A-4) Refer to Chart A.

To a stirred solution of 532 mg ofthe title product of Preparation 2 in 7 mL of methanol at 0°C is added a mixture of 80 mg of lithium hydroxide and 0.6 mL of 30% hydrogen peroxide in 1.6 mL of water. The reaction mixture is allowed to warm to room temperature and, after 30 min, acidified with 1 M aqueous potassium hydrogen

sulfate and then extracted with dichloromethane. The organic phase is dried (magnesium sulfate) and then concentrated. The residue is flashed chromatographed on silica gel with 15% to 25% ethyl acetate in hexane to give 268 mg of the title product.

Physical characteristics of the title product are as follows:

^{1}H-NMR ($CDCl_3$) δ 0.9, 1.45, 1.53, 1.56, 2.6, 3.93, 4.02.

FAB MS $[M+H]^+$=402; $[M+Na]^+$=424.

Preparation 4 — 5-[5S-[3-(*tert*-Butyloxycarbonyl)-2,2-dimethyl-4S-isobutyl-5S-oxazolidinyl]-4S-isobutyl-2-oxazolidinone (Formula A-5) Refer to Chart A.

To a stirred solution of 40 mg of the title product of Preparation 3 in 1 mL of dry tetrahydrofuran under argon is added 0.019 mL of diisopropylethyl amine and 0.024 mL of diphenylphosphoryl azide. The resulting mixture is heated in an oil bath at 70°C. After 3 h, the cooled reaction mixture is concentrated and the residue is chromatographed on silica gel with 20% ethyl acetate in dichloromethane to give 38.2 mg of the title product.

Physical characteristics of the title product are as follows:

^{1}H-NMR ($CDCl_3$) δ 0.9, 1.49, 1.56, 1.58, 4.0, 4.7, 6.70.

FAB HRMS $(M+H)^+$ 399.2863.

IR 3250, 2950, 1760, 1680, 1370 cm^{-1}.

Preparation 5 — 1-[1S-[3-(*tert*-Butyloxycarbonyl)-2,2-dimethyl-4S-isobutyl-5S-oxazolidinyl]-2S-amino-4-methyl-1-pentanol (Formula A-6) Refer to Chart A.

To a stirred solution of 122 mg of the title product of Preparation 4 in 1.5 mL of dioxane is added a solution of 500 mg of $Ba(OH)_2.8H_2O$ in 1.5 mL of water. The resulting mixture is heated to reflux for 3 days, and the cooled reaction mixture is diluted with dichloromethane and water, and then filtered through Celite. The aqueous phase is extracted with dichloromethane. The organic phase is dried (magnesium sulfate) and then concentrated. The residue is chromatographed on silica gel with 2% to 4% methanol (saturated with ammonia) in dichloromethane to give 102.8 mg of the title product.

Physical characteristics of the title product are as follows:

^{1}H-NMR ($CDCl_3$) δ 0.9, 1.48, 1.56, 1.58, 2.8, 3.7, 4.0.

FAB MS $[M+H]^+$=373.

Preparation 6 4S,7S-Diamino-5S,6S-dihydroxy-2,9-dimethyldecane(Formula A-7) Refer to Chart A.

A solution of 0.07 mL of acetyl chloride in 1 mL of methanol is allowed to stirred for 15 min, and then 28.4 mg of the title product of Preparation 5 is dissolved in. After stirring for 24 h, the reaction mixture is concentrated and the resulting residue is dried to give 22 mg of the title product.

Example 1 4S,7S-Di-*tert*-Butyloxycarbonylamino-5S,6S-dihydroxy-2,9-dimethyldecane (Formula A-8) Refer to Chart A.

A mixture of 22 mg of the title product of Preparation 6, 0.032 mL of diisopropylethyl amine and 37 mg of di-*tert*-butyl dicarbonate in 1 mL of dichloromethane is allowed to stir for 24 h. The concentrated reaction mixture is then chromatographed on silica gel with 20% to 25% ethyl acetate in dichloromethane to give 22.8 mg of the title product.

Physical characteristics of the title product are as follows:

^{1}H-NMR ($CDCl_3$) δ 0.92, 1.2, 1.43, 1.7, 3.3, 3.69, 3.91, 4.52.

^{13}C NMR ($CDCl_3$) δ 21.50, 23.69, 24.91, 28.33, 40.91, 50.71, 73.05, 80.02, 157.20.

FAB HRMS $[M+H]^+$ 433.3290.

Example 2 4S,7S-Bis-[N^{α}-*tert*-Butyloxycarbonyl-L-valyl-amino]-5S,6S-dihydroxy-2,9-dimethyldecane (Formula A-9) Refer to Chart A.

To a stirred mixture of 15.3 mg of the title product of Preparation 6 and 26 mg of *tert*-butyloxycarbonyl-L-valine in 0.5 mL of dichloromethane at 0°C is added 0.047 mL of diisopropylethyl amine and 0.018 mL of diethylphosphoryl cyanide. The resulting mixture is allowed to stir at room temperature for 18 h, and the concentrated reaction mixture is then chromatographed on silica gel with 1:1 = ethylacetate : dichloromethane to give 21.4 mg of the title product.

Physical characteristics of the title product are as follows:

^{1}H-NMR ($CDCl_3$) δ 0.9, 1.44, 2.1, 3.32, 3.83, 4.0, 5.05, 6.26.

FAB HRMS $[M+H]^+$ = 631.4655.

Preparation 7 4S,7S-Bis-[N^{α}-*tert*-Butyloxycarbonyl-N^{im}-tosyl-L-histidyl-amino]-5S,6S-dihydroxy-2,9-dimethyldecane(Formula B-2) Refer to Chart B.

To a stirred mixture of 22.9 mg of the title product of Preparation 6 and 74 mg

of *tert*-butyloxycarbonyl-N^{im}-tosyl-L-histidine in 0.8 mL of dichloromethane at 0°C is added 0.058 mL of diisopropylethyl amine and 0.028 mL of diethylphosphoryl cyanide. The resulting mixture is allowed to stir at room temperature for 18 h, and the concentrated reaction mixture is then chromatographed on silica gel with 3% to 5% methanol in dichloromethane to give 49.4 mg of the title product .

Physical characteristics of the title product are as follows:

^{1}H-NMR ($CDCl_3$) δ 0.9, 1.42, 2.46, 2.8, 3.60, 5.6, 5.65, 6.64, 7.1, 7.40, 7.77, 7.84.

FAB MS $[M+H]^+ = 1015$.

Preparation 8 4S,7S-Bis-[1-Naphthoxyacetyl-N^{im}-tosyl-L-histidyl-amino]-5S,6S-dihydroxy-2,9-dimethyldecane (Formula B-3) Refer to Chart B.

A solution of 49.4 mg of the title product of Preparation 7 in 0.5 mL of 1:1 = trifluoroacetic acid : dichloromethane is allowed to stir for 50 min. The reaction mixture is partitioned between dichloromethane and aqueous sodium bicarbonate. The organic phase is dried (sodium sulfate) and then concentrated to give 42.6 mg.

To a stirred solution of this residue and 23.6 mg of 1-naphthoxyacetic acid in 0.5 mL of dichloromethane at 0°C is added 0.020 mL of diisopropylethyl amine and 0.018 mL of diethylphosphoryl cyanide. The mixture is allowed to stir at room temperature for 18 h, and the concentrated reaction mixture is then chromatographed on silica gel with 3% to 5% methanol in dichloromethane to give 49.3 mg of the title product.

Physical characteristics of the title product are as follows:

^{1}H-NMR ($CDCl_3$) δ 0.63, 0.65, 0.8, 1.1-1.4, 2.31, 2.88, 3.12, 3.33, 4.0, 4.70, 4.77, 4.88, 6.49, 6.87, 6.91, 7.2 - 7.7, 7.86, 8.42, 8.81.

FAB MS $[M+H]^+ = 1183$.

Example 3 4S,7S-Bis-[1-Naphthoxyacetyl-L-histidyl-amino]-5S,6S-dihydroxy-2,9-dimethyldecane (Formula B-4) Refer to Chart B.

A solution of 49.3 mg of the title product of Preparation 8 and 34 mg of 1-hydroxybenzotriazole in 0.5 mL of methanol is allowed to stir for 18 h. The concentrated reaction mixture is then chromatographed on silica gel with 4% to 8% methanol (saturated with ammonia) in dichloromethane to give 32.6 mg, of the title product.

Physical characteristics of the title product are as follows:

^{1}H-NMR ($CDCl_3$) δ 0.8, 1.3, 3.0, 3.72, 4.18, 4.63, 4.8, 6.27, 6.71, 7.3-7.5,

7.77, 8.30.

FAB HRMS $[M+H]^+$ =875.4466.

Preparation 9 4-Methylvaleric acid, 2,6-dimethylphenol ester (Formula C-2) Refer to Chart C.

4.4 g of 60% sodium hydride in oil is washed with four portions of hexane and the resulting residue is suspended in 200 mL of dry ether. To this stirred mixture at 0°C is slowly added a solution of 12.2 g of 2,6-dimethylphenol in 25 mL of dry ether. After complete addition, a solution of 15.2 mL of 4-methylvaleryl chloride in 25 mL of dry ether is added dropwise. The resulting mixture is allowed to warm to room temperature and stir overnight. The reaction mixture is diluted with cold water and the organic phase washed successively with diluted aqueous potassium hydroxide, water, diluted aqueous HCl, and then saturated aqueous sodium chloride. The organic phase is dried (magnesium sulfate) and then concentrated, and the residue is distilled at ca. 0.2 mmHg, 75-76°C to give a colorless liquid, 20.88 g of the title product.

Physical characteristics of the title product are as follows:

^{1}H-NMR ($CDCl_3$) δ 1.00 1.7, 2.17, 2.6, 7.1.

Preparation 10 3-[3R-[3-(*tert*-Butyloxycarbonyl)-2,2-dimethyl-4S-isobutyl-5R-oxazolidinyl]-3-hydroxy-2S-isobutylpropionic acid, 2,6-dimethylphenol ester (Formula C-3 (A) and (B)) Refer to Chart C.

To a stirred solution of 0.3 mL of diisopropylamine in 1.5 mL of dry tetrahydrofuran at -78°C under argon is slowly added 1.3 mL of a 1.56 M solution of butyllithium in hexane. After 5 min, a solution of 441 mg of the title product of preparation 9 in 0.5 mL of dry tetrahydrofuran is added dropwise. After 1 h, a solution of 571 mg of the aldehyde C-1 in 0.5 mL of dry tetrahydrofuran is slowly added. After 1 h, 5 mL of saturated aqueous ammonium chloride is added and the resulting mixture allowed to warm to room temperature. It is diluted with water and then extracted with ether. The organic phase is dried (magnesium sulfate) and then concentrated, and the residue is chromatographed on silica gel with 15% to 20% ethyl acetate in hexane to give 300 mg of the title product, 156 mg of the other diastereomer and 220 mg of mixed fractions.

Physical characteristics of the title product are as follows:

^{1}H-NMR ($CDCl_3$), δ 1.0, 1.50, 1.55, 1.61, 2.20, 3.3, 3.61, 3.8, 4.1.

FAB MS $[M+H]^+$ = 506.

Physical characteristics of the other diastereomer are as follows:

^{1}H NMR δ 1.0, 1.50, 2.16, 2.9, 3.3, 3.7-4.3, 7.0

Preparation 11 3-[3R-[3-(*tert*-Butyloxycarbonyl)-2,2-dimethyl-4S-isobutyl-5R-oxazolidinyl]-3-hydroxy-2S-isobutylpropionic acid (Formula C-4 (A)) Refer to Chart C.

To a stirred solution of 300 mg of the title product of Preparation 10 in 0.6 mL of methanol is added a solution of 160 mg of potassium hydroxide in 0.6 mL of water and 0.6 mL of methanol. The resulting mixture is stirred for 18 h, and then partitioned between water and ether. The aqueous phase is acidified with 1 M aqueous potassium hydrogen sulfate and then extracted with dichloromethane. The organic phase is dried (magnesium sulfate) and then concentrated, and the residue is chromatographed on silica gel with 10% to 15% methanol in dichloromethane to give 195 mg of the title product.

Physical characteristics of the title product are as follows:

^{1}H-NMR ($CDCl_3$) δ 0.9, 1.48, 1.54, 1.55, 2.95, 3.5, 3.7, 4.1.

Preparation 12 5-[5R-[3-(*tert*-Butyloxycarbonyl)-2,2-dimethyl-4S-isobutyl-5R-oxazolidinyl]-4S-isobutyl-2-oxazolidinone (Formula C-5) Refer to Chart C.

To a stirred solution of 100 mg of the title product of Preparation 11 in 1.5 mL of dry tetrahydrofuran under argon is added 0.048 mL of diisopropylethylamine, followed by 0.059 mL of diphenylphosphoryl azide. The resulting mixture is heated to reflux for 5 h. The cooled reaction mixture is partitioned between dichloromethane and water. The organic phase is dried (magnesium sulfate) and then concentrated, and the residue is chromatographed on silica gel with 15% to 20% ethyl acetate in dichloromethane to give 91.6 mg of the title product.

Physical characteristics of the title product are as follows:

^{1}H-NMR ($CDCl_3$) δ 0.9, 1.46, 3.8, 4.0, 6.77.

FAB MS $[M+H]^+$ =399.

Preparation 13 1-[1R-[3-(*tert*-Butyloxycarbonyl)-2,2-dimethyl-4S-isobutyl-5R-oxazolidinyl]-2S-amino-4-methyl-1-pentanol (Formula C-6) Refer to Chart C.

To a stirred solution of 91 mg of the title product of Preparation 12 in 1.2 mL of dioxane is added a solution of 400 mg of $Ba(OH)_2.8H_2O$ in 0.8 mL of water. The resulting mixture is heated to reflux for 3 days, and the cooled reaction mixture is partitioned between dichloromethane and water. The organic phase is dried (magnesium

sulfate) and then concentrated, and the residue is chromatographed on silica gel with 1% to 3% methanol (saturated with ammonia) in dichloromethane to give 76.6 mg of the title product.

Physical characteristics of the title product are as follows:

^{1}H-NMR ($CDCl_3$) δ 0.9, 1.3, 1.48, 1.53, 3.3, 3.6, 4.1.

FAB MS $[M+H]^+$ =373.

Preparation 14 4S,7S-Diamino-5R,6R-dihydroxy-2,9-dimethyldecane(FormulaC-7) Refer to Chart C.

A solution of 0.07 mL of acetyl chloride in 1 mL of methanol is allowed to stirred for 15 min, and then 76 mg of the title product of Preparation 13 is dissolved in. After stirring for 24 h, the reaction mixture is concentrated and the resulting residue is dissolved in 2 mL of water. This solution is then lyophilized to give 53.9 mg of the title product.

Physical characteristics of the title product are as follows:

^{1}H NMR (D_2O) δ 0.90, 1.5, 1.66, 3.50, 3.81

^{13}C NMR (D_2O) δ 21.40, 21.98, 23.89, 38.44, 50.67, 69.65.

FAB MS $[M+H]^+$ =233.

Example 4 4S,7S-Bis-[N^{α}-*tert*-Butyloxycarbonyl-L-valyl-amino]-5R,6R-dihydroxy-2,9-dimethyldecane (Formula C-8) Refer to Chart C.

To a stirred solution of 15 mg of the title product of Preparation 14 and 25.6 mg of *tert*-butyloxycarbonyl-L-valine in 0.5 mL dimethylformamide is added 0.038 mL of diisopropylethylamine and 48 mg of bis(2-oxo-3-oxazolidinyl)phosphinic chloride. After stirring for 18 h, the concentrated reaction mixture is chromatographed on silica gel with 3% to 5% methanol in dichloromethane to give 31 mg of the title product.

Physical characteristics of the title product are as follows:

1H-NMR ($CDCl_3$) δ 0.9, 1.25, 1.41, 1.6, 2.1, 2.45, 3.1, 3.86, 3.95, 4.2, 5.22, 5.40, 6.8.

FAB HRMS $[M+H]^+$ 631.4631

Examples 5-9

Following chemical processes and procedures analogous to those described above and using starting materials and reactants which are commerically available or readily prepared by methods known in the art, the following compounds of the present invention, having the indicated physical characteristics, are prepared:

Example 5 4S,7R-Di-tert-butyloxycarbonylamino-5R,6S-dihydroxy-2,9-dimethyldecane. FAB-MS (found): 433.3269.

Example 6 4S,7R-Bis-[N^{α}-tert-Butyloxycarbonyl-L-valyl-amino]-5R,6S-dihydroxy-2,9-dimethyldecane. FAB-MS (found): 631.4649.

Example 7 4S,7S-Bis-[N^{α}-Benzyloxycarbonyl-L-valyl-amino]-5R,6R-dihydroxy-2,9-dimethyldecane. FAB-MS (found): 699.4337.

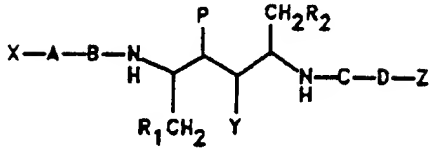
Example 8 4S,7S-Bis-[N^{α}-Benzyloxycarbonyl-L-valyl-amino]-5S,6S-dihydroxy-2,9-dimethyldecane. FAB-MS (found): 699.4337.

Example 9 4S,7S-Bis-[N^{α}-Benzyloxycarbonyl-L-valyl-amino]-5R,6S-dihydroxy-2,9-dimethyldecane. FAB-MS (found): 699.4337.

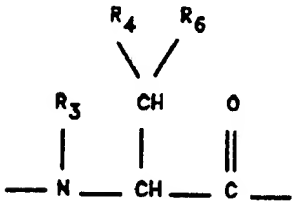
TABLE I

Compound of Example Number	HIV Protease Inhibitor Activity K_I(nM)
1	>0.4
2	0.65
3	1.1
4	>1
5	>1
6	>1
7	>1
8	0.29
9	0.58

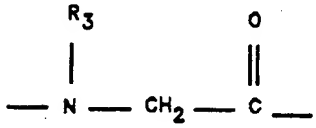
FORMULA CHART



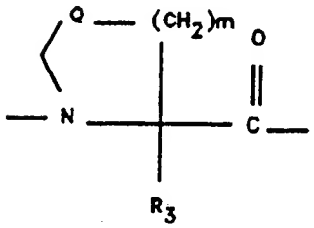
I



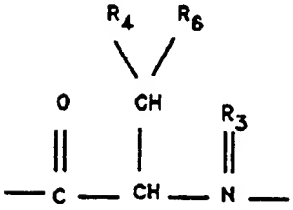
XL_1



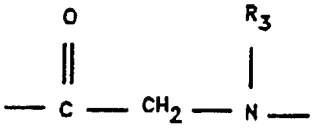
XL_2



XL_3

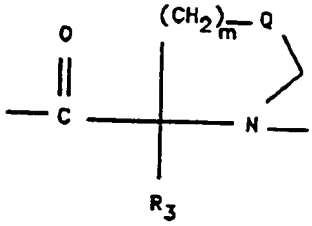


XL_4



XL_5

FORMULA CHART (continued)



XL_6

CHART A

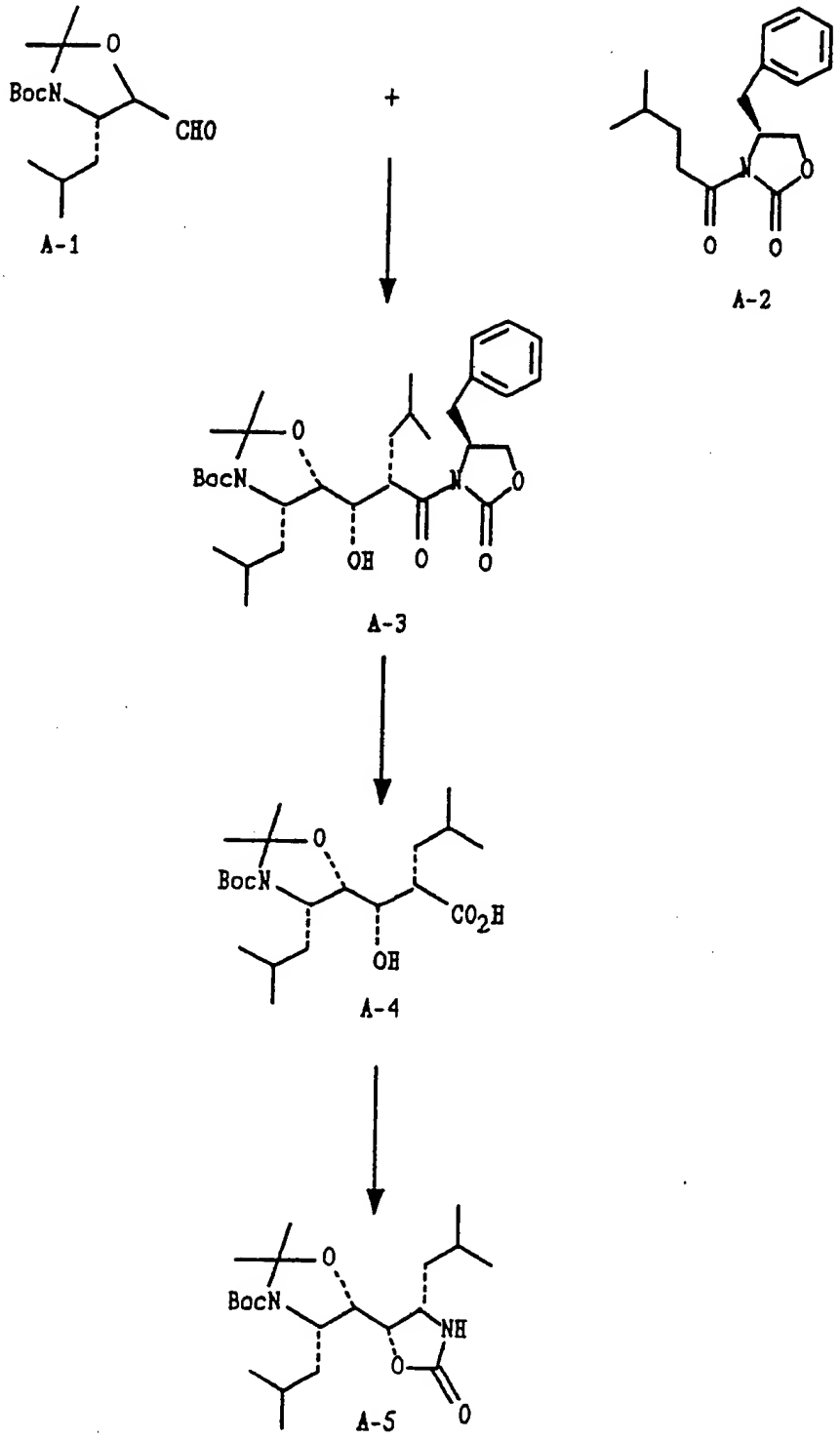


CHART A (continued)

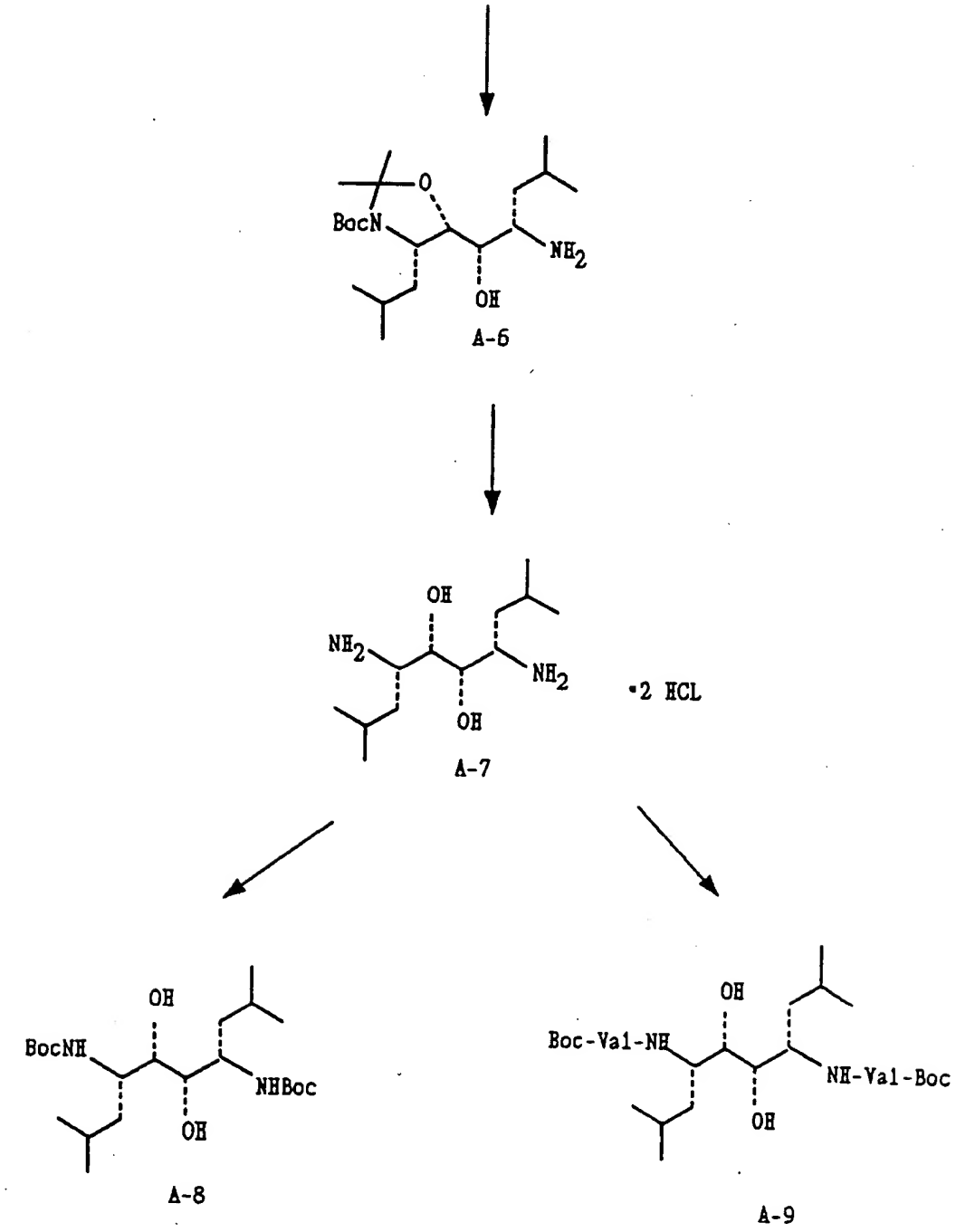


CHART B

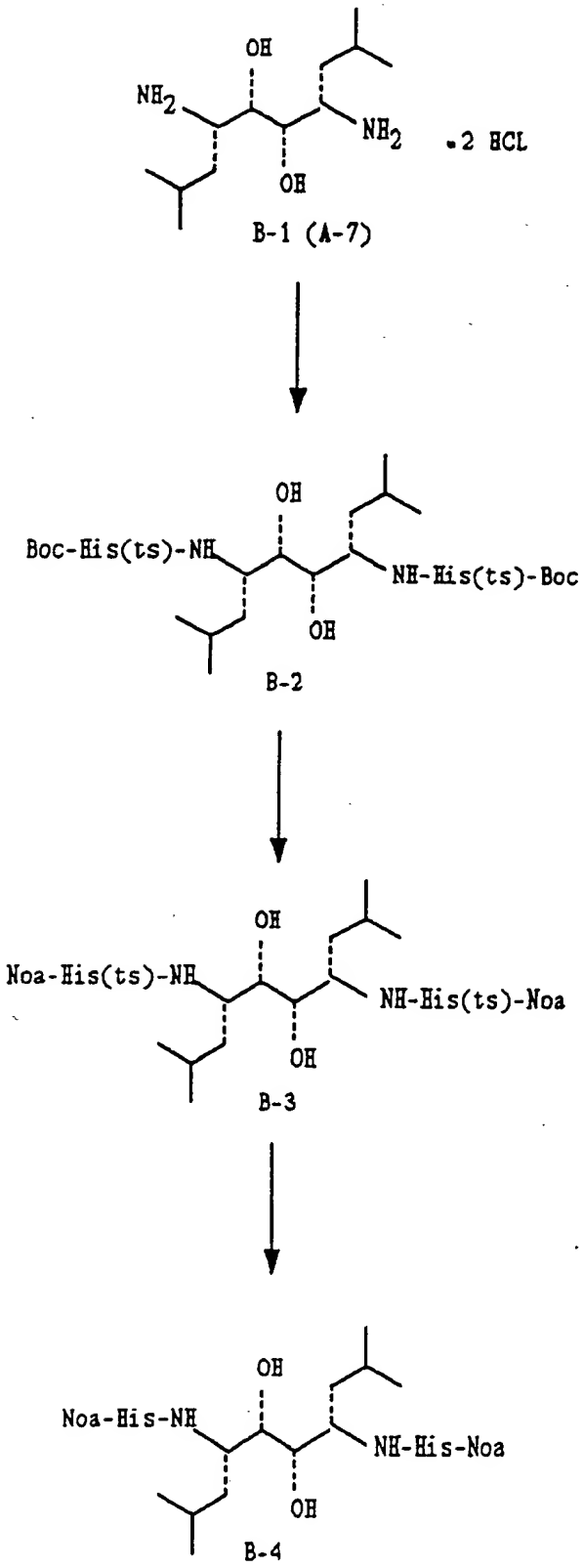

OH
NH2
NH2
• 2 HCL
OH
B-1 (A-7)
OH
Boc-His(ts)-NH
NH-His(ts)-Boc
OH
B-2
OH
Noa-His(ts)-NH
NH-His(ts)-Noa
OH
B-3
OH
Noa-His-NH
NH-His-Noa
OH
B-4

CHART C

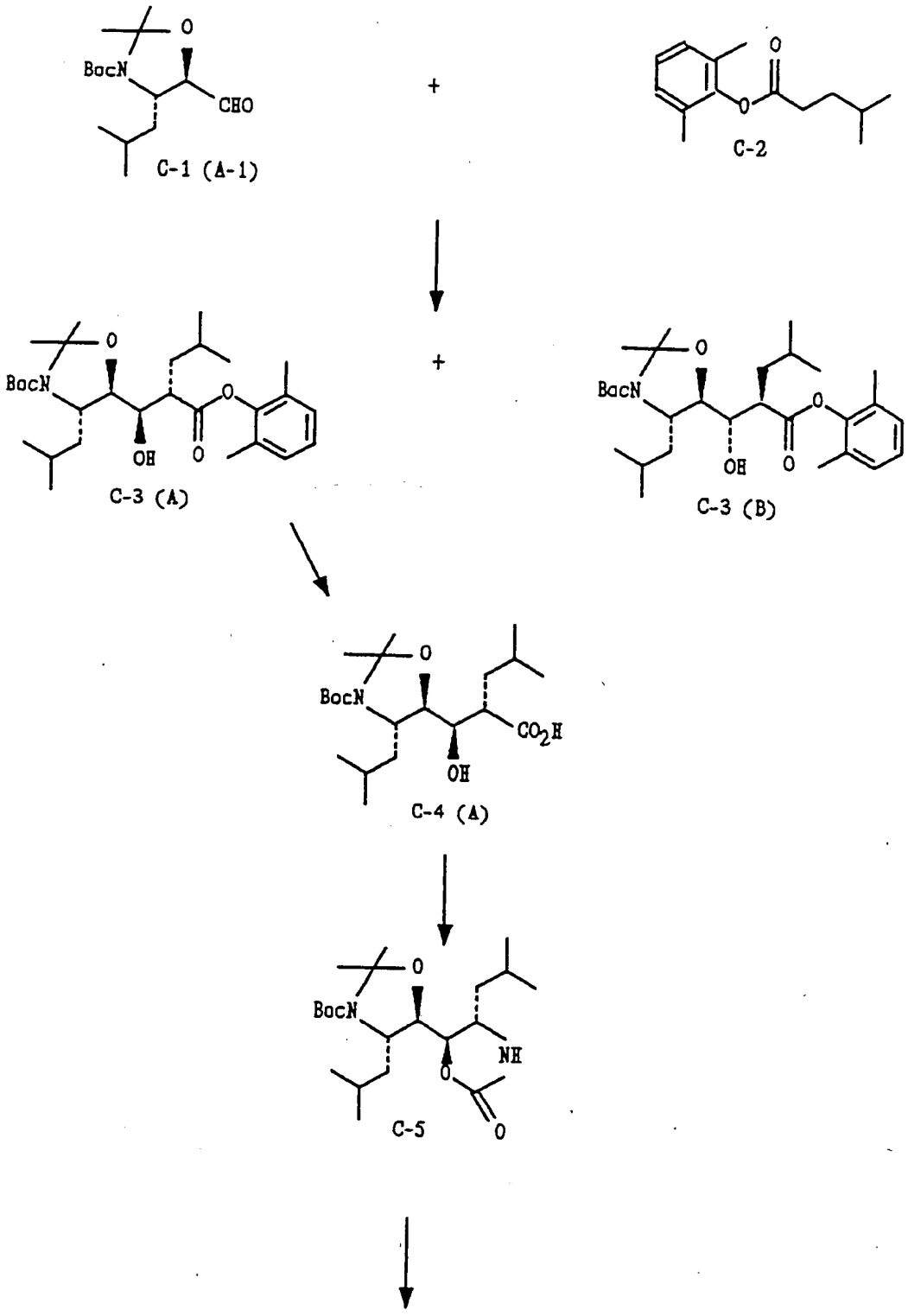
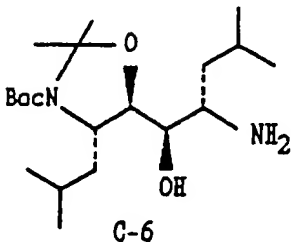
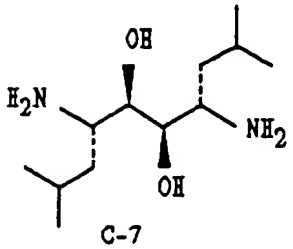

BocN
CHO
C-1 (A-1)
+
C-2
BocN
OH
C-3 (A)
+
BocN
OH
C-3 (B)
BocN
CO_2H
OH
C-4 (A)
BocN
NH
C-5

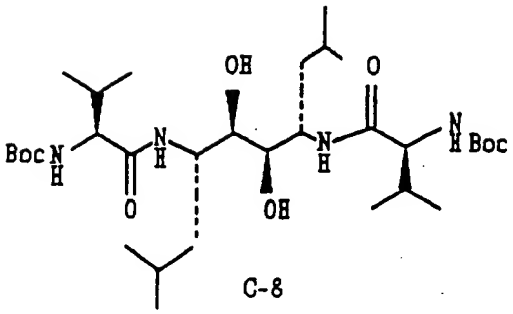
CHART C (continued)



C-6



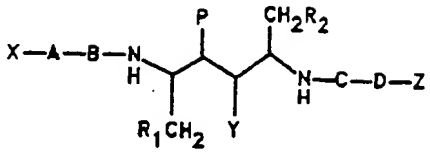
C-7



C-8

CLAIMS

1. A compound of Formula I



I

wherein X is

(a) hydrogen,

(b) C_1-C_7alkyl,

(c) aryl-$(CH_2)_p$-,

(d) Het-$(CH_2)_p$-,

(e) C_3-C_7cycloalkyl-$(CH_2)_p$-,

(f) R_5-O-CH_2-C(O)-,

(g) R_5-CH_2-O-C(O)-,

(h) R_5-O-C(O)-,

(i) R_5-$(CH_2)_n$-C(O)-,

(j) R_5-$(CH_2)_n$-C(S)-,

(k) $R_4N(R_4)$-$(CH_2)_n$-C(O)-

(l) R_5-SO_2-$(CH_2)_q$-C(O)-,

(m) R_5-SO_2-$(CH_2)_q$-O-C(O)-,

(n) R_6-$(CH_2)_n$-C(O)-, or

(o) R_5-$(CH_2)_n$-SO_2-;

wherein Z is

(a) hydrogen,

(b) C_1-C_7alkyl,

(c) -$(CH_2)_p$-aryl,

(d) -$(CH_2)_p$-Het,

(e) -$(CH_2)_p$-C_3-C_7cycloalkyl,

(f) -C(O)-CH_2-O-R_5,

(g) -C(O)-O-CH_2-R_5,

(h) -C(O)-O-R_5,

(i) -C(O)-$(CH_2)_n$-R_5,

(j) -C(S)-$(CH_2)_n$-R_5,

(k) $-C(O)-(CH_2)_n-(R_4)NR_4$,

(l) $-C(O)-(CH_2)_q-SO_2-R_5$,

(m) $-C(O)-O-(CH_2)_q-SO_2-R_5$,

(n) $-C(O)-(CH_2)_n-R_6$, or

(o) $-SO_2-(CH_2)_n-R_5$;

wherein P is OH or NH_2;

wherein Y is OH or NH_2;

wherein Q is

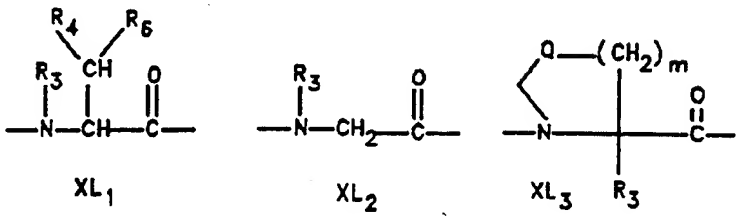
(a) $-CH_2-$,

(b) -CH(OH)-,

(c) -O-, or

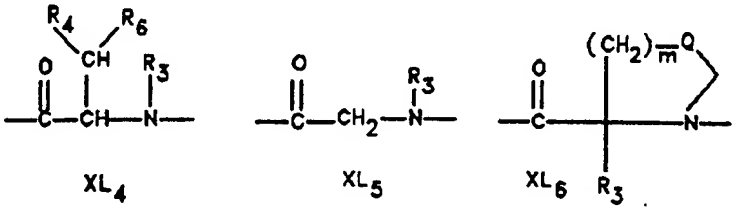
(d) -S-;

wherein A or B or both are absent or are a divalent moiety of the formula XL_1, XL_2 or XL_3 or other amino acyl derivative;



XL_1 XL_2 XL_3

wherein C or D or both are absent or are a divalent moiety of the formula XL_4, XL_5 or XL_6 or other amino acyl derivative;



XL_4 XL_5 XL_6

wherein R_1 is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) aryl,

(d) C_3-C_7cycloalkyl,

(e) -Het,

(f) C_1-C_3alkoxy, or

(g) C_1-C_3alkylthio;

wherein R_2 is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) aryl,

(d) C_3-C_7cycloalkyl,

(e) -Het,

(f) C_1-C_3alkoxy, or

(g) C_1-C_3alkylthio;

wherein R_3 is

(a) hydrogen,

(b) C_1-C_5alkyl, or

(c) aryl-C_1-C_5alkyl;

wherein R_4 is

(a) hydrogen

(b) C_1-C_5alkyl,

(c) -$(CH_2)_p$-aryl,

(d) -$(CH_2)_p$-Het,

(e) -$(CH_2)_p$-C_3-C_7cycloalkyl, or

(f) 1- or 2-adamantyl;

wherein R_5 is

(a) C_1-C_6alkyl,

(b) -$(CH_2)_p$-C_3-C_7cycloalkyl,

(c) -$(CH_2)_p$-aryl,

(d) -$(CH_2)_p$-Het, or

(e) 5-oxo-2-pyrrolidinyl;

wherein R_6 is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) -$(CH_2)_p$-aryl,

(d) -$(CH_2)_p$-Het,

(e) -$(CH_2)_p$-C_3-C_7cycloalkyl, or

(f) 1- or 2-adamatyl;

wherein R_7 is

(a) hydrogen,

(b) C_1-C_3alkyl, or

(c) phenyl-C_1-C_3alkyl;

wherein R_8 is

(a) hydrogen,

(b) C_1-C_5 alkyl, or

(c) -$(CH_2)_p$-phenyl;

wherein m is 1 to 2, inclusive

wherein n is 0 to 5, inclusive;

wherein p is 0 to 2, inclusive;

wherein q is 1 to 5, inclusive;

wherein aryl is phenyl or naphthyl substituted by zero to three of the following:

(a) C_1-C_3alkyl,

(b) hydroxy,

(c) C_1-C_3alkoxy,

(d) halo,

(e) amino,

(f) mono- or di-C_1-C_3alkylamino,

(g) -CHO,

(h) -COOH,

(i) $COOR_7$,

(j) $CONHR_7$,

(k) nitro,

(l) mercapto,

(m) C_1-C_3alkylthio,

(n) C_1-C_3alkylsulfinyl,

(o) C_1-C_3alkylsulfonyl,

(p) -$N(R_8)$-C_1-C_3alkylsulfinyl,

(q) SO_3H,

(r) SO_2NH_2,

(s) -CN, or

(t) CH_2NH_2;

wherein -Het is a 5- or 6-membered saturated ring containing from one to three

heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another heterocycle; and if chemically feasible, the nitrogen and sulfur atoms may be in the oxidized forms; and optionally substituted by zero to three of the following:

(a) C_1-C_5alkyl,

(b) hydroxy,

(c) hydroxy (C_1-C_5alkyl),

(d) halogen,

(e) amino,

(f) amino (C_1-C_5alkyl),

(g) -CHO,

(h) -CO_2H,

(i) -CO_2-(C_1-C_5alkyl),

(j) -$CONH_2$,

(k) -CONH-(C_1-C_5alkyl),

(l) nitro,

(m) mercapto,

(n) mercapto (C_1-C_5alkyl),

(o) -SO_3H,

(p) -SO_2NH_2,

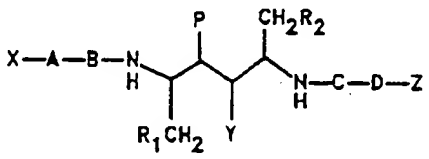
(q) -CN, or

(r) -O-C_1-C_5alkyl;

or a carboxy, amino or other reactive group protected form thereof;

or a pharmaceutically acceptable acid or base addition salt thereof.

2. A compound of Formula I of claim 1



I

wherein X is

(a) hydrogen,

(b) C_1-C_7alkyl,

(c) aryl-$(CH_2)_p$-,

(d) Het-$(CH_2)_p$-,

(e) C_3-C_7cycloalkyl-$(CH_2)_p$-,

(f) R_5-O-CH_2-C(O)-,

(g) R_5-CH_2-O-C(O)-,

(h) R_5-O-C(O)-,

(i) R_5-$(CH_2)_n$-C(O)-,

(j) R_5-$(CH_2)_n$-C(S)-,

(k) $R_4N(R_4)$-$(CH_2)_n$-C(O)-

(l) R_5-SO_2-$(CH_2)_q$-C(O)-,

(m) R_5-SO_2-$(CH_2)_q$-O-C(O)-,

(n) R_6-$(CH_2)_n$-C(O)-, or

(o) R_5-$(CH_2)_n$-SO_2-;

wherein Z is

(a) hydrogen,

(b) C_1-C_7alkyl,

(c) -$(CH_2)_p$-aryl,

(d) -$(CH_2)_p$-Het,

(e) -$(CH_2)_p$-C_3-C_7cycloalkyl,

(f) -C(O)-CH_2-O-R_5,

(g) -C(O)-O-CH_2-R_5,

(h) -C(O)-O-R_5,

(i) -C(O)-$(CH_2)_n$-R_5,

(j) -C(S)-$(CH_2)_n$-R_5,

(k) -C(O)-$(CH_2)_n$-$(R_4)NR_4$,

(l) -C(O)-$(CH_2)_q$-SO_2-R_5,

(m) -C(O)-O-$(CH_2)_q$-SO_2-R_5,

(n) -C(O)-$(CH_2)_n$-R_6, or

(o) -SO_2-$(CH_2)_n$-R_5;

wherein P is OH or NH_2;

wherein Y is OH or NH_2;

wherein Q is

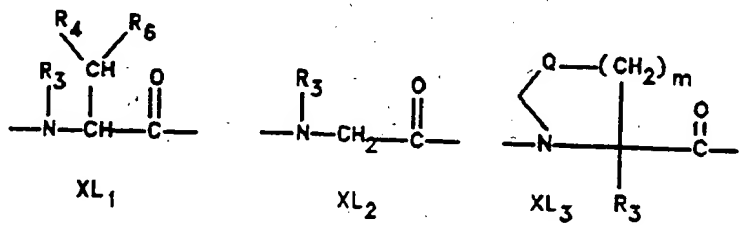
(a) -CH_2-,

(b) -CH(OH)-,

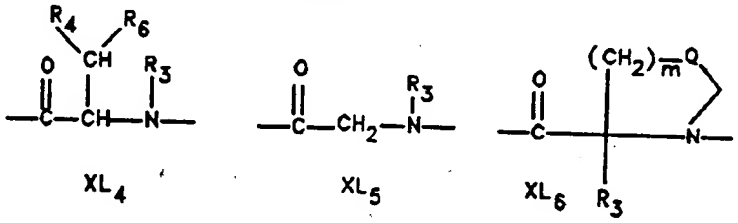
(c) -O-, or

(d) -S-;

wherein A or B or both are absent or are a divalent moiety of the formula XL_1, XL_2 or XL_3 or other amino acyl derivative;



wherein C or D or both are absent or are a divalent moiety of the formula XL_4, XL_5 or XL_6 or other amino acyl derivative;



wherein R_1 is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) aryl,

(d) C_3-C_7cycloalkyl,

(e) -Het,

(f) C_1-C_3alkoxy, or

(g) C_1-C_3alkylthio;

wherein R_2 is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) aryl,

(d) C_3-C_7cycloalkyl,

(e) -Het,

(f) C_1-C_3alkoxy, or

(g) C_1-C_3alkylthio;

wherein R_3 is

(a) hydrogen,

(b) C_1-C_5alkyl, or

(c) aryl-C_1-C_5alkyl;

wherein R_4 is

(a) hydrogen

(b) C_1-C_5alkyl,

(c) -$(CH_2)_p$-aryl,

(d) -$(CH_2)_p$-Het,

(e) -$(CH_2)_p$-C_3-C_7cycloalkyl, or

(f) 1- or 2-adamantyl;

wherein R_5 is

(a) C_1-C_6alkyl,

(b) -$(CH_2)_p$-C_3-C_7cycloalkyl,

(c) -$(CH_2)_p$-aryl,

(d) -$(CH_2)_p$-Het, or

(e) 5-oxo-2-pyrrolidinyl;

wherein R_6 is

(a) hydrogen,

(b) C_1-C_5alkyl,

(c) -$(CH_2)_p$-aryl,

(d) -$(CH_2)_p$-Het,

(e) -$(CH_2)_p$-C_3-C_7cycloalkyl, or

(f) 1- or 2-adamatyl;

wherein R_7 is

(a) hydrogen,

(b) C_1-C_3alkyl, or

(c) phenyl-C_1-C_3alkyl;

wherein R_8 is

(a) hydrogen,

(b) C_1-C_5 alkyl, or

(c) -$(CH_2)_p$-phenyl;

wherein m is 1 to 2, inclusive

wherein n is 0 to 5, inclusive;

wherein p is 0 to 2, inclusive;

wherein q is 1 to 5, inclusive;

wherein aryl is phenyl or naphthyl substituted by zero to three of the following:

(a) C_1-C_3alkyl,

(b) hydroxy,

(c) C_1-C_3alkoxy,

(d) halo,

(e) amino,

(f) mono- or di-C_1-C_3alkylamino,

(g) -CHO,

(h) -COOH,

(i) $COOR_7$,

(j) $CONHR_7$,

(k) nitro,

(l) mercapto,

(m) C_1-C_3alkylthio,

(n) C_1-C_3alkylsulfinyl,

(o) C_1-C_3alkylsulfonyl,

(p) -N(R_8)-C_1-C_3alkylsulfinyl,

(q) SO_3H,

(r) SO_2NH_2,

(s) -CN, or

(t) CH_2NH_2;

wherein -Het is a 5- or 6-membered saturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another heterocycle; and if chemically feasible, the nitrogen and sulfur atoms may be in the oxidized forms; and optionally substituted by zero to three of the following:

(a) C_1-C_5alkyl,

(b) hydroxy,

(c) hydroxy (C_1-C_5alkyl),

(d) halogen,

(e) amino,

(f) amino (C_1-C_5alkyl),

(g) -CHO,

(h) -CO_2H,

(i) -CO_2-(C_1-C_5alkyl),

(j) -$CONH_2$,

(k) -CONH-(C_1-C_5alkyl),

(l) nitro,

(m) mercapto,

(n) mercapto (C_1-C_5alkyl),

(o) -SO_3H,

(p) -SO_2NH_2,

(q) -CN, or

(r) -O-C_1-C_5alkyl;

or a carboxy, amino or other reactive group protected form thereof;

or a pharmaceutically acceptable acid or base addition salt thereof.

with the provisos that:

1) R_1 and R_2 are each other than phenyl when X and Z are each t-butyloxycarbonyl, A, B, C and D are absent and P and Y are each hydroxy; and

2) R_1 and R_2 are each other than phenyl when X and Z are each benzyloxycarbonyl, A and D are absent, B and C are each Val, and P and Y are each hydroxy.

3. A compound of claim 2

wherein X is

(a) t-butyloxycarbonyl,

(b) 1-naphthoxyacetyl, or

(c) benzyloxycarbonyl;

wherein Z is

(a) t-butyloxycarbonyl,

(b) 1-naphthoxyacetyl, or

(c) benzyloxycarbonyl;

wherein P is OH;

wherein Y is OH;

wherein A is absent;

wherein B is

(a) valyl, or

(b) histidyl;

wherein C is

(a) valyl, or

(b) histidyl;

wherein D is absent;

wherein R_1 is isopropyl;

wherein R_2 is isopropyl.

4. A compound of claim 3 selected from the group consisting of:

4S,7S-Di-*tert*-Butyloxycarbonylamino-5S,6S-dihydroxy-2,9-dimethyldecane;

4S,7S-Bis-[N^{α}-*tert*-Butyloxycarbonyl-L-valyl-amino]-5S,6S-dihydroxy-2,9-dimethyldecane;

4S,7S-Bis-[1-Naphthoxyacetyl-L-histidyl-amino]-5S,6S-dihydroxy-2,9-dimethyldecane;

4S,7S-Bis-[N^{α}-*tert*-Butyloxycarbonyl-L-valyl-amino]-5R,6R-dihydroxy-2,9-dimethyldecane;

4S,7R-Di-tert-butyloxycarbonylamino-5R,6S-dihydroxy-2,9-dimethyldecane;

4S,7R-Bis-[N^{α}-tert-Butyloxycarbonyl-L-valyl-amino]-5R,6S-dihydroxy-2,9-dimethyldecane;

4S,7S-Bis-[N^{α}-Benzyloxycarbonyl-L-valyl-amino]-5R,6R-dihydroxy-2,9-dimethyldecane;

4S,7S-Bis-[N^{α}-Benzyloxycarbonyl-L-valyl-amino]-5S,6S-dihydroxy-2,9-dimethyldecane;

4S,7S-Bis-[N^{α}-Benzyloxycarbonyl-L-valyl-amino]-5R,6S-dihydroxy-2,9-dimethyldecane.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/07047

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 K 5/06, 5/02; C 07 C 271/20 // A 61 K 37/64

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	A 61 K; C 07 C; C 07 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	J. Med. Chem., vol. 33, No. 10, 1990, Ronald B. Gammill et al: "Structure-Based, C2 Symmetric Inhibitors of HIV Protease ", see page 2687 - page 2689	1-4
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P,X	EP, A2, 0393445 (BAYER AG) 24 October 1990, see the whole document	1-4
	--	
P,X	EP, A2, 0428849 (HOECHST AG) 29 May 1991, see the whole document	1-4
	--	
P,A	WO, A1, 9101327 (THE UPJOHN COMPANY) 7 February 1991, see the whole document	1-4
	--	

* Special categories of cited documents:[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
10th February 1992	27.02.92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	E. R. VONK

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	WO, A1, 8804664 (THE UPJOHN COMPANY) 30 June 1988, see the whole document	1-4

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/US 91/07047

SA 52968

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 31/10/91 The European Patent office is in no way liable for theseparticulars which are merely given for the purpose of information.

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EP-A2- 0393445	24/10/90	DE-A-	3912829	25/10/90
		JP-A-	2304028	17/12/90
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		CN-A-	1050545	10/04/91
		DE-A-	4030350	11/04/91
		JP-A-	3120245	22/05/91
WO-A1- 9101327	07/02/91	AU-D-	6066390	22/02/91
WO-A1- 8804664	30/06/88	AU-D-	1243888	15/07/88
		EP-A-	0344189	06/12/89